REMARKS

In the Claims:

Claims 22-24 and 30-31 have been cancelled without prejudice or disclaimer.

Claims 25-26 have been amended to clarify that the claimed nucleic acid encodes a polypeptide which stimulates release of proteoglycans from cartilage tissue. No new matter is added by this amendment, and it is supported at pages 137-138 of the specification.

Claims 28-29 and 32-34 have been rewritten in independent form and no longer depend from rejected Claim 27. Therefore Applicants respectfully submit that Claims 28-29 and 32-34 are in condition for allowance.

Claim 35 has been amended to clarify that the claimed nucleic acid hybridizes under high stringency conditions. Support for this amendment may be found at page 30, lines 12-21 of the specification.

Claim 36 has been amended to clarify what conditions may qualify as high stringency conditions. Support for this amendment may be found at page 30, lines 12-21 of the specification.

Claim 37 has been amended to clarify that the isolated nucleic acid of Claim 35 is at least 35 nucleotides in length. Support for this amendment may be found at page 64, lines 12-37 of the specification.

Claims 38-41 have been amended to clarify that the vector and host cell referred to therein are isolated. Support for this amendment may be found at pages 112-115 of the specification.

Claims 42 and 43 are newly added herein. New claims 42 and 43 do not encompass new matter and are supported at pages 59-62 of the specification.

Priority

Applicants agree with the Examiner's factual determination that the subject matter defined in this application is supported by the disclosure in U.S. Application Serial No. 09/254,311, filed on March 3, 1999, which is a 35 U.S.C. § 371 of PCT/US98/25108, filed on December 1, 1998. Accordingly, Applicants also agree that the claimed subject matter has an effective filing date of December 1, 1998.

Information Disclosure Statement

The Examiner states that the IDS filed on April 29, 2002 is incomplete and therefore was not considered it on its merits, but did not state what information would cure the "incomplete" status. Applicants herein submit a revised PTO-1449 form for the application that is compliant with 37 C.F.R. § 1.97(c)(2), including that Applicants herein tender the fee set forth in 37 C.F.R. § 1.17(p). As required by 37 C.F.R. § 1.98(b)(5), the enclosed PTO-1449 names each citation with specificity and discloses the date, number of pages, the author, as well as the GenBank Accession number. Thus, Applicants respectfully request that this IDS be considered on its merits in accordance with MPEP § 609.

Claim rejections under 35 U.S.C. § 112, first paragraph

Enablement:

The Examiner rejected Claims 22-41 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for an isolated nucleic acid having 80%-99% amino acid sequence identity or hybridizing to the nucleic acid encoding the polypeptide of SEQ ID NO: 2 or to the nucleic acid sequence of SEQ ID NO:1. Claims 22-24 have been cancelled without prejudice or disclaimer. Thus, currently pending Claims 25-41

are alleged to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is mostly connected, to make and/or use the invention.

As noted by the Examiner, Applicants have disclosed a function for PRO241, namely the stimulation of release of proteoglycans from cartilage tissue (specification page 137, Example 29). This function has both diagnostic and therapeutic applications, known to those skilled in the art.

With respect to the specific elements of Claims 25-26, claiming an isolated nucleotide having at least 95%-99% amino acid sequence identity to the nucleic acid encoding the polypeptide of SEQ ID NO:2 or the nucleic acid sequence of SEQ ID NO:1, pages 59-62 of the specification describe several methods for preparing or synthesizing the claimed polynucleotide variants and fragments. Therefore, the specification, together with other methods known in the art, enables the skilled artisan without undue experimentation to prepare or synthesize the variant nucleic acid sequences recited in Claims 25-26. Moreover, in keeping with the Examiner's recommendation, the amended Claims 25-26 now include a functional limitation, reciting the ability of the polypeptide encoded by each claimed construct to stimulate release of proteoglycans from cartilage tissue.

As described at pages 137-138 of the specification, one of ordinary skill in the art is enabled to assay whether a polypeptide falls within the scope of Claims 25-26. In addition to using standard techniques for determining the claimed sequence identity, whether a polypeptide is capable of stimulation of release of proteoglycans from cartilage tissue can be assessed using the assay described in the protocol. One of the standards for enablement is to make certain the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 731, 737 (Fed. Cir. 1988).

Moe specifically, the assay described at pages 137-138 of the specification involves treating a sample of cartilage with the polypeptide of appropriate sequence identity

being tested, then using a standard colorimetric assay to quantitatively determine proteoglycan release. The color intensity of the experimental sample is compared to the control to determine whether and how effectively the polypeptide being tested was able to stimulate release of proteoglycans. The colorimetric assay is described in "Improved quantitation and discrimination of sulphated glycosaminoglycans by use of dimethylmethylene blue" Farndale, *et al.* Biochim Biophys Acta. 883(2):173-177 (1986), which is incorporated by reference in the instant application. The assay is based on a metachromatic shift in absorption maximum which occurs when dimethylene blue dye is complexed with sulfated glycosaminoglycans including proteoglycans. The specific shift allows quantitation of the proteoglycan concentration from fluid around the cartilage. The presence of proteoglycans in proximity with cartilage, including in the synovial lining of joints, is known to be important in joint mobility. Other assays, or variants of the disclosed assay, sufficient to measure stimulation of proteoglycan release from cartilage are known and practiced in the art, and the present description is tendered only as one means of measuring that activity for the species embraced by the instant application.

Because of the known clinical usefulness of proteoglycan release from cartilage, the species embraced by Claims 25-26 have application to treatment of injuries and diseases affecting cartilage including sports-related joint problems, articular cartilage defects, rheumatoid arthritis, and osteoarthritis, as described in the specification at page 138.

Applicants respectfully disagree with the Examiner that the claims encompass an unreasonable number of inoperative polypeptides which the skilled artisan would not know how to use. While Applicants agree with the Examiner and the cited references that, on occasion, even a single modification or substitution in a protein sequence can alter protein function, one of skill in the art would recognize that many polypeptides have conserved amino acids, or active sites and it is modifications affecting these conserved amino acids that can result in altered protein function. (*See generally* Lewin, "Genes VII" *at* Parts 1-4, Oxford University Press, 2000).

Further, one of skill in the art will also recognize that there are numerous nucleic acids, encoding *non-conserved* amino acids that could be changed in a sequence without substantially altering the structure, physiological function, or activity of the encoded polypeptide. Even further, one of skill in the art would also recognize that even some conserved amino acids can be substituted without significant adverse effect upon the function of the polypeptide because even extensively changing the amino acid or nucleic acid sequence may still result in polypeptides that retain many epitopes unique to the wild type polypeptide. At page 61 (Table 6 and accompanying text) of the instant specification, Applicants suggest several methods for substituting amino acids in various sequences, while still conserving the structure and function of the encoded wild-type polypeptide, binding properties, *etc.* For instance, using site-directed mutagenesis, PCR mutagenesis, and other techniques described at page 61, lines 43-48, a practitioner in the art would be able to introduce desired conservative or non-conservative amino acid substitutions, yet maintain PRO241 functionality.

The skilled artisan would recognize that variants and fragments of PRO241 would have the same or similar utility to full length polypeptides in detecting, monitoring, or preparing applications using PRO241. While some degree of routine experimentation might possibly be necessary to perform the substitutions of nucleotides and determine the functionality of the modified PRO241-based polypeptides, this does not mean the claims are not enabled. Even a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed.Cir. 1988). According to the MPEP § 2164.01, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." The manipulations described in the specification comprise routine practice in the art (*See generally* Sambrook, *et al.*, "Molecular Cloning: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 2001 (offering support for the proposition that techniques such as site-directed mutagenesis, PCR mutagenesis, and other techniques described at page 61, lines 43-48, are commonplace in the art)).

Regarding independent Claim 27, the Examiner states that the specification is enabling for an isolated nucleic acid encoding the polypeptide of SEQ ID NO:2. Since the Examiner has proffered no basis for rejection of this claim under § 112, Applicants respectfully request withdrawal of the rejection of Claim 27. In addition, Applicants request that the Examiner withdraw the rejection of amended Claims 28-29 and 32-34, which, like Claim 27, are independent and recite the fully disclosed sequences shown in Figures 1 and 2 of the specification (SEQ ID NO:1 and SEQ ID NO:2).

The Examiner also rejects Claims 35-37 alleging that there is no recitation of the full set of conditions used for hybridization. Furthermore, the Examiner alleges that the specification does not demonstrate a function for the polypeptide, nor is it clear what the polynucleotide would be used for. Thus, the Examiner opines that one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Applicants have amended Claim 35 to reflect that the hybridization of the nucleic acid occurs under high stringency conditions. One example of such high stringency hybridization conditions is set forth at page 30, lines 17-21 of the instant specification. Amended Claim 36 sets forth specific high stringency conditions. Amended Claim 37 reflects that the claimed polynucleotide hybridizing under high stringency conditions must be at least 35 nucleotides in length. The hybridization reaction under the claimed conditions is well-known in the art. Therefore, amended Claims 35-37 overcome the stated grounds for rejection and Applicants request that the rejection be withdrawn.

The Examiner states that the "no art teaches the instantly claimed nucleic acids or analogues." Applicants respectfully note that the uniqueness of the claimed matter is precisely why they are pursuing a patent. However, the Examiner also uses this statement to allege that "skill in this area of work is not high." In the same context, the Examiner also notes that an art disclosed after the effective filing date of the instant application (Lorenzo *et al.*) teaches a nucleic acid identical to that claimed herein, but does not disclose any information on how to make and use the instant genus of nucleic

acids. The stated purpose of the Lorenzo *et al.* reference was merely descriptive, and the lack of information on how to make and use a biglycan-related protein in that reference reflects its limited scope rather than a lack of skill in the art amongst practitioners.

The Examiner does not specifically state the grounds for rejection of Claims 38-41 other than the blanket rejection of Claims 22-41 at the top of the Office Action, page 6. During examination, "*each claim must be separately analyzed* and given its broadest reasonable interpretation in light of and consistent with the written description." *See, e.g.*, In re Morris, 127 F.3d 1048, 1053-54 (Fed.Cir. 1997). *See also* MPEP § 2163 (8th ed. 2001)(emphasis added). Also, "[i]n rejecting a claim, the *examiner must set forth express findings of fact which support the lack of written description conclusion* (internal reference omitted). These findings should: (A) *identify the claim limitation at issue*" MPEP § 2163.04 (8th ed. 2001)(emphasis added). The Examiner's rejection does not offer a separate analysis that identifies each claim limitation at issue. However, Applicants have endeavored to answer with all possible detail, on a claim-by-claim basis, the rejections and objections set forth by the Examiner.

Claims 38-41 were included in the Examiner's rejection alleging failure to enable under 35 U.S.C. § 112, first paragraph. Applicants have amended Claims 38-41 to clarify that the vector and host cell referred to therein are isolated. Examples 20-22 on pages 111-115 of the instant specification provide disclosure sufficient to enable one skilled in the art to practice Claims 38-41 as amended. Accordingly, Applicants request that any rejection of Claims 38-41 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Applicants respectfully ask that, based upon the foregoing remarks, the Examiner withdraw all rejection of Claims 25-41.

Written Description

The Examiner rejected Claims 22-41 under 35 U.S.C. § 112, first paragraph, contending that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

The written description requirement requires that an applicant's specification convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath, Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed.Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula . . . of the claimed subject matter ***sufficient to distinguish it from other materials***. *Univ. of Calif. v. Eli Lilly & Co.,* 43 USPQ2d 1398, 1405 (Fed.Cir. 1997) (emphasis added). Since one skilled in the art can distinguish a described formula from other formulas and therefore can ***identify many of the species*** that the claims encompass, a described formula is normally an adequate description of the claimed invention. *Id.* at 1406 (emphasis added). Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, first paragraph, "Written Description" Requirement ("the Guidelines"), "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) *Fed. Reg.* at 1107; 191 USPQ at 97.

Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed.Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow*, 217 USPQ 1089 (Fed.Cir. 1991). Moreover, in order to have possession of members of a claimed genus, the specification ***need not*** describe all of the species that the genus encompasses. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1027 (Fed.Cir. 1991).

In view of the legal standard regarding the written description requirement under 35 U.S.C. § 112, first paragraph, in combination with the interpretation of the written description requirement by the United States Patent and Trademark Office as set forth in the Guidelines, Applicants respectfully submit that the instant specification satisfies the written description requirement. It would be clear to one of skill in the art that Applicants possessed the claimed subject matter at the time of filing the instant application. For example, several structural features, such as open reading frames, the translation initiation site, and predicted polypeptide precursors of the cDNA sequence of PRO241, are disclosed at lines 6-14 on page 94 of the specification. A host of PRO241 features disclosed in Figure 2 describe the polypeptide in great detail. For example, some of the PRO241 features described are conserved structures forming different protein domains: a signal sequence; an N-glycosylation site; N-myristoylation sites; and a leucine zipper pattern (Figure 2). A skilled artisan would easily recognize start and stop codons, leucine rich repeats, a relationship to the various biglycan proteoglycan proteins, and other signatures and homologies of the non-coding regions of the DNA34392-1170 encoding the PRO241 polypeptide.

The Examiner also alleges that the claims are drawn to a genus of inoperative polynucleotides that is defined only by sequence identity or hybridization, and that the claims do not describe any particular biological activity, conserved structure, or other disclosed distinguishing feature that is associated with PRO241.

Applicants respectfully disagree that the specification fails to describe any particular biological activity, conserved structure, or other disclosed distinguishing feature. In fact, at page 142, line 15, in Table 24, the specification discloses expression patterns associated with PRO241 (DNA34392-1170), including tissues where PRO241 nucleic acids are significantly expressed and tissues where they are not. At page 137, line 29, through page 138, line 11, the specification discloses the ability of PRO241 to stimulate the release of proteoglycans from cartilage tissue. Thus, Applicants submit that the claimed genus is not only defined by sequence identity.

More specifically, Claims 25-26, as amended, are directed to isolated nucleic acids that each encode a polypeptide that stimulates the release of proteoglycans from cartilage tissue and that have at least 95% or 99% sequence identity to (a) the nucleic acid encoding the polypeptide shown in Figure 2 (SEQ ID NO:2); (b) the nucleic acid sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), lacking its associate signal peptide; (c) the nucleic acid sequence shown in Figure 1 (SEQ ID NO:1); (d) the full-length coding sequence of the nucleic acid sequence shown in Figure 2 (SEQ ID NO:1); or (e) the full-length coding sequence of the cDNA deposited under ATCC accession number 209526. As such, Claims 25-26 require that the genus of nucleic acids encompassed within the claims not have substantial variation from the disclosed species that is actually reduced to practice in the specification (*i.e.*, SEQ ID NO: 1) in that the claimed nucleic acids must possess at least 95% or 99% sequence identity to the recited polynucleotide sequences.

The current application is in compliance with the Guidelines. The analysis for determining whether the present specification provides written description support for the invention defined by Claims 25-26 may be performed by numerous methods, several of which are described in the Guidelines and further exemplified in the Revised Interim Written Description Guidelines Training Materials ("Written Description Training Materials"), published on the USPTO website at http://www.uspto.gov/web/offices/pac/writtendesc.pdf (a complete copy of which is enclosed herewith as Exhibit A). These Written Description Training Materials provide additional clarity to the Guidelines published in the Federal Register, Volume 66, No. 4, pages 1099-1111. In fact, as indicated in the USPTO press release of March 1, 2000 (Press Release #00-15), these training materials were promulgated by the USPTO and are:

> "designed to aid PTO's patent examiners in applying the interim written description and utility guidelines in a uniform and consistent manner to promote the issuance of high quality patents. The training materials will also assist patent

applicants in responding to the PTO when utility or written description issues are raised during the examination of a patent application." (emphasis added)

With regard to amended Claims 25-26, the present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials (Exhibit A). More specifically, in Example 14 on pages 53-55 of the enclosed Written Description Training Materials, a claim directed to a protein and variants thereof having 95% sequence identity, all of which share the same biological function, is analyzed for its compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. The Written Description Training Materials conclude that such a claim satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, when (1) a single protein sequence is actually reduced to practice, (2) procedures for making variants of that "reduced to practice" protein sequence are conventional in the art, and (3) an assay is described which allows identification of other proteins having the same biological activity. The reasoning provided by the USPTO in the Written Description Training Materials is that:

> "[t]here is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:...does not have substantial variation since all of the variants must possess the specified [biological function] and must have at least 95% identity to the reference sequence, SEQ ID NO:...The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:...which are capable of the specified [biological function]. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.....{As such], the disclosure meets the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention." (Exhibit A at pages 54-55) (emphasis added).

All of the just-mentioned requirements are met by this application as well as the currently pending claims. In particular, amended Claims 25-26 are supported by the specification, which discloses a representative nucleic acid of the claimed genus (Figures 1 and 2), procedures that are conventional in the art for making variants (pages 59-63), and assays which allow identification of other species having the same biological activity (pages 137-138).

Applicants have amended their claims to parallel exactly the example provided in the Written Description Training Materials: as amended, the claims embrace only members of the claimed genus having 95% or 99% sequence identity. Analogous to Example 14 of the Written Description Training Materials, the present specification discloses and actually reduces to practice the nucleic acid sequence that is recited in amended Claims 25-26 (*i.e.*, SEQ ID NO:1) as well as a single polypeptide sequence encoding PRO241 (*i.e.*, SEQ ID NO:2). Moreover, the nucleic acid variants encompassed within amended Claims 25-26 ***do not have substantial variation*** with SEQ ID NO:1 because they share at least 95% or 99% sequence identity with SEQ ID NO:1 or the nucleic acid encoding the polypeptide sequence of SEQ ID NO:2. (Methods for routinely determining nucleic acid and/or amino acid sequence identity are described in detail in the present specification at page 23, line 34 to page 29, line 2; *see also* pages 34-54 illustrating means for displaying nucleic acids encoding polypeptides having these biological functions). As such, the nucleic acids encompassed within Claims 25-26 all share substantial common structural features (*i.e.*, 95% or 99% sequence identity). Moreover, the present specification also describes conventionally known methods used and known in the art for preparing a multitude of nucleic acid variants (see the present specification at page 59, line 13 to page 63, line 36).

Given the abovementioned factors, Applicants respectfully submit that Claims 25-26 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, because the specification provides "a precise definition, such as by structure, formula . . . of the claimed subject matter *sufficient to distinguish it from other materials*" as required by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed.Cir.

1997). Moreover, Claims 25-26 are analogous to the claim found to satisfy the written description requirement in Example 14 of the enclosed Written Description Training Materials. *See* Appendix A. As such, under the Guidelines and the examination training materials promulgated by the USPTO for ensuring consistent examination of written description compliance during prosecution of patent applications, the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied for Claims 25-26. Therefore, Applicants respectfully request this ground of rejection be withdrawn.

Claim 27 is drawn to the isolated nucleic acid sequence disclosed in the specification as shown in Figure 1 (SEQ ID NO:1). The Examiner states on page 9 of the instant Office Action that the "isolated nucleic acid encoding the polypeptide of SEQ ID NO:2 (including the nucleic acid of SEQ ID NO:1) ... meets the written description requirement provision of 35 U.S.C. § 112, first paragraph." Since the Examiner did not proffer a written description basis for rejection, Applicants respectfully request that the rejection of Claim 27 be withdrawn.

The Examiner rejected Claims 35-37 on the basis that no specific hybridization conditions were claimed such that non-specific hybridization could occur. Claim 35 has been amended to specify hybridization under "high stringency conditions," and Claim 36 has been amended to specify an exemplary set of conditions for "high stringency." Claim 37 has been amended to require hybridization of a polynucleotide at least 35 nucleotides in length, thereby increasing the hybridization specificity. Consonant with the law of *Amgen*, *Vas-Cath*, and *Kaslow*, Applicants have conveyed, to one having ordinary skill in the art, possession of the claimed genus. In order to have possession of members of a claimed genus, the specification need not describe all of the species that the genus encompasses. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1027 (Fed.Cir. 1991). Applicants have fully disclosed a representative of the claimed genus (Figures 1-2 of the specification), and have described the methods for deriving the claimed species (pages 12-21 and 59-64 of the specification). Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed, but the description must allow a person of ordinary

skill in the art to recognize that she invented what is claimed. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed.Cir. 1991). Applicants have clarified high stringency conditions for hybridization such that one of ordinary skill in the art has sufficient disclosure to practice the claimed species. Applicants submit that the present disclosure satisfies the test as to whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow*, 217 USPQ 1089 (Fed.Cir. 1991). Therefore, Applicants request that the rejection of Claims 35-37 be withdrawn.

The Examiner's rejection of Claims 22-41 includes vectors and host cells recited in Claims 38-41 comprising the nucleic acid recited in Claim 22. Claims 38-41 have been amended to clarify that the respective vector or cell is isolated and now depend upon Claim 25. This amendment is supported by Examples 20-23 on specification pages 111-116. Applicants respectfully propose that the claims as amended, together with the above specification-supported remarks (addressed to the written description rejection for alleged failure to demonstrate possession) are sufficient to answer the Examiner's rejection by demonstrating possession of the claimed subject matter.

Thus, Applicants submit that Claims 25-41 are adequately described in the specification, sufficient to comply with 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of the rejection of Claims 25-41 on the basis of alleged failure to demonstrate possession of the claimed invention.

Claim rejections under 35 U.S.C. § 112, second paragraph:

Claims 22-27, 30, 31 and 35-41 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the recitation of "extracellular domains" in these claims is indefinite since the protein identified as PRO241 with the amino acid sequence set forth in SEQ ID NO:2 is a soluble protein and is not disclosed as being expressed on the cell surface. Applicants have amended currently pending Claims 25-27 and 35-41 to clarify that the polypeptide encoded by the claimed nucleic acid does not comprise an extracellular domain. Applicants have also cancelled Claims

30-31. Accordingly, Applicants submit that they have overcome the rejection for indefiniteness to Claims 25-27 and 35-41 and request that the rejection to those claims be withdrawn.

The Examiner asserts that Claim 36 is indefinite because it recites "'under stringent conditions', without defining the hybridization conditions in the claims." As the Examiner notes, on page 30 of the instant specification, lines 12-21, Applicants define "stringent conditions" or "high stringency conditions." Applicants provide exemplary hybridization and wash conditions as part of this definition. Furthermore, Applicants have amended Claim 36 to clarify that the claimed nucleic acid hybridizes under high stringency conditions. As explained at lines 17-21, on page 30 of the specification and in Claim 36, as amended, one example of high stringency conditions includes employing 50% formamide, 5 x SSC (0.75 M sodium chloride, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

Applicants have amended Claim 36 as discussed above, and Claim 37, which depends upon Claim 36 is modified accordingly. Therefore, Applicants submit that they have overcome this rejection of Claim 36 and respectfully request it be withdrawn.

Claim rejections under 35 U.S.C. § 102

The Examiner rejected Claims 35-37 under 35 U.S.C. § 102(b) as being anticipated by Dreher *et al.* (GENEMBL, Accession No. U17834, January 5, 1995). The Examiner contends that Dreher *et al.* teach a 24-nucleotide sequence encoding eight amino acids of SEQ ID NO:2 that would, by its nature, hybridize to the nucleic acid sequence encoding SEQ ID NO:2.

Applicants have amended Claims 35-37. Applicants submit that the teachings in the Dreher *et al.* reference fall outside of amended Claims 35-37, which clarify that hybridization occurs under "high stringency conditions." The 24 nucleotide sequence described by the Examiner from the Dreher *et al.* reference would be unable to hybridize to the disclosed nucleic acid sequence under high stringency conditions. One skilled in the art may conduct standard calculations to determine the percent sequence identity required for hybridization (See Sambrook, *et al.*, "Molecular Cloning: A Laboratory Manual" Cold Spring Harbor Laboratory Press, 2001, pp.10.1-10.10). The isolated nucleic acid molecule comprising DNA encoding a PRO241 polypeptide is 1137 nucleotides long. The overlap between the 1137-nucleotide long PRO241 DNA sequence and the sequence taught by Dreher *et al.* consists of only twenty-four nucleotides that are located at the end of the 3' coding region of the PRO241 DNA. Under the specified high stringency conditions, one of ordinary skill in the art will recognize that the 24-nucleotide sequence recited in Dreher *et al.* would not hybridize to the polynucleic acid encoding SEQ ID NO:2. Therefore, Claims 35-37 are not anticipated by the teaching of the Dreher *et al.* reference. Applicants submit that they have overcome this basis for rejection of Claims 35-37 and respectfully request that this ground of rejection be withdrawn.

Claim Objection

Claims 28-29 and 32-34 were objected to as being dependent upon rejected base claims. Rejected Claims 28-29 and 32-34 were drawn to the isolated nucleic acid sequence of Claim 27 which recites the isolated nucleic acid sequence disclosed in the specification as shown in Figure 1 (SEQ ID NO:1). The Examiner states that Claims 28-29 and 32-34 "would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." Amended Claims 28-29 and 32-34 are now submitted in independent form, including the relevant limitations of Claim 27. Based upon that statement by the Examiner and Applicants' remarks above, Applicants respectfully request that the objection to Claims 28-29 and 32-34 be withdrawn.

Conclusion

Applicants believe that currently pending Claims 25-29 and 32-41 are patentable. Applicants respectfully request that the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite the prosecution this application.

Respectfully submitted,

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